REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully traversed.

The objection to claims 1, 13, 28, 29, and 44-45, because they contain non-elected subject matter is respectfully traversed in view of the above amendments. To the extent this objection is maintained with regard to new claims 55-58, applicants' respectfully disagree. The February 28, 2002, written restriction requirement deemed the use of various factors to be separate inventions. In response, applicants elected invention Group I which related to the use of brain-derived neurotrophic factor, neurotrophin-4/5, and neurotrophin-3. Although invention Group III which related to the use of noggin was not elected, that action does not preclude applicants from now claiming the combination of brain-derived neurotrophic factor and noggin. The combination of brain-derived neurotrophic factor and noggin in new claims 55-58 was never raised in the previously-imposed restriction requirement nor in the applicant's responsive election. Therefore, it cannot be said that applicants made an election that excluded the subject matter of the new claims. On the contrary, the combination of brain-derived neurotrophic factor and noggin in new claims 55-58 is entirely consistent with what applicants previously elected. Accordingly, these claims should now receive a full examination.

The rejection of claims 28-30, 33-38, 44-46, and 49 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

It should be noted that the claims 28 and 44 are directed to treating (rather than curing) a neurodegenerative disease or condition. Therefore, it is improper to base any enablement rejection of the claimed subject matter on a lack of data demonstrating the curing of such a disease or conditions. As explained *infra*, applicants have fully demonstrated that the claimed invention is effective in treating neurodegenerative diseases or conditions—nothing more is required by 35 U.S.C. § 112 (1st para.).

The accompanying Third Declaration of Steven A. Goldman, M.D., Ph.D. Under 37 C.F.R. § 1.132 ("Third Goldman Declaration") further demonstrates that the claimed invention is highly effective in treating a neurodegenerative disease. In particular, this data shows that the effect of AdBDNF alone and AdBDNF/AdNoggin delayed functional deterioration and the effect of AdBDNF alone and AdBDNF/AdNoggin on survival.

Motor coordination and balance were measured using rotarod analysis (Andreassen et al., *Neurobiol Dis* 8:479 (2001)) (Third Goldman Declaration ¶ 6). AdBDNF/AdNoggin (n=10), AdBDNF (n=17) and AdNull (n=19) treated R6/2 mice were assessed by rotarod, as were untreated controls (n-17), beginning at 4 weeks of age (*Id.*). The mice were trained three times daily for two consecutive days on a rotarod (7650, UGO basile, Biological Research Apparatus, VA, Italy), at a constant speed of 12 rpm; they were subsequently tested weekly at the same speed (*Id.*). At each weekly test, each mouse was given three trials on the rod, and their latencies to fall measured. A maximum latency was defined at 300 sec., at which the individual test was terminated and scored as 300 sec.; for every 3-trial test, the best result, i.e., the longest time spent on the rod without falling, was recorded (*Id.*). All mice were tested from the day before stereotaxic surgery, at 4 weeks of age, until either 13 weeks of age, or until they were unable to maintain their body posture, whichever was later (*Id.*). Rotarod scores of <60 sec were considered neurologically abnormal (Laforet et al., *J. Neurosci* 21:9112 (2001)) (*Id.*). This criterion was used to define impairment, the incidence of which was evaluated weekly (*Id.*). Comparisons of the mean duration of rotarod performance as a function of age were performed by ANOVA, followed by post-hoc Bonferroni t-tests (*Id.*).

To assess the effect of AdBDNF/AdNoggin-injection upon the functional deterioration of R6/2 mice, both rotarod testing and open-field analysis of volitional locomotion were used (Third Goldman Declaration ¶ 7). It was also examined whether AdBDNF/AdNoggin co-treatment, which yields substantially more neuronal recruitment than that afforded by AdBDNF alone, resulted in better motor performance than that achieved solely by BDNF (Canals et al., *J. Neuroscience* 24:7727 (2004)) (*Id.*). All mice were trained on the rod by 4 weeks of age, and then tested weekly at a constant 12 rpm (Andreassen et al., *Neurobiol Dis* 8:479 (2001)) (*Id.*). It was found that the AdBDNF/AdNoggin-treated mice exhibited a significant deceleration in motor deterioration, relative to AdNull-treated R6/2 controls (attached Figure 1A) (*Id.*). When the latency to fall off the rotarod (y) was plotted as a function of post-operative survival (m), curves were generated for AdBDNF/AdNoggin- and AdNull-injected mice that appeared to diverge at approximately 5 weeks after treatment (*Id.*). Simple regression analysis revealed that whereas the motor performance of AdBDNF/AdNoggin-treated animals could be described by the line $y = -28.5x + 321.6$, that of their AdNull-treated controls was described by $y = 44.7x + 318.2$ (*Id.*). ANOVA of these regressions revealed that the rate of deterioration of motor performance, as reflected in the regression slopes, was significantly influenced by treatment ($F=4.68$ [3, 68 df]; $p=0.005$) (*Id.*). Post hoc analysis showed that the

rate of motor deterioration was significantly greater in AdNull-injected R6/2 mice than in either their AdBDNF/AdNoggin or AdBDNF-treated counterparts (p=0.008 and 0.024, respectively) (*Id.*).

When rotarod performance was compared between groups at each time point, again using ANOVA with post hoc tests, it was found that by 7 weeks after treatment, the AdBDNF/AdNoggin-injected R6/2s performed significantly better than their AdNull and untreated controls (p=0.007 and 0.012, respectively) (Third Goldman Declaration). In addition, the AdBDNF/AdNoggin-treated R6/2s exhibited a performance advantage over mice treated only with AdBDNF, which achieved statistical significance by 9 weeks post-treatment, at 13 weeks of age (p=0.003) (attached Figure 1A) (*Id.*). When assessed with regard to their ability to sustain 60 sec of rotarod performance, the AdBDNF/AdNoggin-treated R6/2 mice performed significantly better than their controls by 11 weeks of age, or 7 weeks after viral injection (p = 0.001; F=6.14 [3, 52 df]) (*Id.*). This difference was sustained through 13 weeks of age (p = 0.001; F=6.55 [3, 32 df]); post hoc comparisons thereafter became difficult as the control animals died, yielding a disproportionate representation of AdBDNF/AdNoggin-treated animals; rotarod testing was halted at that point (*Id.*). Similarly, open-field testing revealed that net locomotion was relatively preserved in AdBDNF/AdNoggin-treated R6/2 mice, which exhibited significantly more volitional horizontal explorative behavior than either their null controls or AdBDNF-treated mice at 13 weeks of age (p=0.012; F=4.39 [3, 29 df]) (attached Figure 1B) (*Id.*).

Importantly, the increments in both 60 sec rotarod or open-field performance measures noted in AdBDNF/AdNoggin-treated mice were not replicated by AdBDNF alone (attached Figures 1A-1B) (Third Goldman Declaration ¶ 9). To the contrary, AdBDNF treatment alone never yielded a significant increment in either measure, relative to AdNull or untreated R6/2 controls (*Id.*). These data suggest that the robust neuronal recruitment associated with AdBDNF/AdNoggin correlated with functional improvement, while the more limited neurogenic and neurotrophic effects of BDNF alone failed to do so (*Id.*).

AdBDNF/AdNoggin, AdBDNF and AdNull-treated R6/2 mice were assessed for viability twice daily beginning at 4 weeks of age (Third Goldman Declaration ¶10). Uninjected R6/2 mice were also included as untreated negative controls (*Id.*). To exclude the possibility that net survival might be affected by rotarod or open-field testing, the mice in the survival study were not subjected to any behavioral assessment (*Id.*). Survival data were analyzed by Kaplan-Meier survival curves (*Id.*).

In light of the motor performance increments noted in AdBDNF/AdNoggin-treated R6/2 mice, it was examined if treatment influenced survival (Third Goldman Declaration ¶ 11). In addition, it was examined if the effects of AdBDNF/Noggin co-treatment were significantly better than those achieved with BDNF alone (*Id.*). To this end, the mean survival of matched groups of R6/2 mice (n=10/group) were compared after being treated at 4 weeks of age with either: 1) a single AdBDNF/Noggin injection; 2) AdBDNF alone; 3) AdNull:GFP control; or 4) no treatment at all (*Id.*). The mice were then returned to their cages and followed, with supportive husbandry until death (*Id.*). It was found that AdBDNF/AdNoggin co-injected R6/2 mice survived significantly longer than both AdBDNF-treated and untreated controls (*Id.*). Moreover, the net survival of AdBDNF-treated R6/2 mice treated with AdBDNF alone was no different than that of their AdNull-treated controls (Figure 1C) (*Id.*). Kaplan-Meier survival analysis by SSPS revealed that AdBDNF/AdNoggin-treated R6/2 mice survived a mean of 110.0 ± 3.3 days, whereas AdNull and untreated controls survived 94.5 ± 3.2 and 96.6 ± 2.7 days, respectively (*Id.*). ANOVA revealed that the overall effect of treatment upon survival was significant ($p=0.011$; $F=4.45$ [3, 38 df]) (*Id.*). Post hoc analysis confirmed the difference in mean survival between AdBDNF/Noggin-treated R6/2s and their AdNull and untreated controls ($p<0.01$ and <0.05 respectively), such that AdBDNF/Noggin-treated R6/2s survived an average of 16.8% longer than their AdNull controls (*Id.*). Although the effect of treatment achieved statistical significance at day 98 ($p=0.013$), it was due largely to the relative survival of AdBDNF/AdNoggin-treated mice; R6/2s treated only with AdBDNF survived 102.0 ± 2.2 days, which was not significantly better than AdNull and untreated R6/2 controls (*Id.*). Thus, the survival benefit associated with AdBDNF/AdNoggin treatment was not provided by AdBDNF alone (Figure 1C) (*Id.*).

Applicants first established that adenoviral overexpression of BDNF induces neuronal recruitment to the neostriatum, from ventricular zone progenitor cells (Third Goldman Declaration ¶ 12). These new neurons invade the bulk of the neostriatum, and differentiate largely if not exclusively as medium spiny neurons (MSNs) (*Id.*). These new MSNs integrate into the normal striatal neuronal architecture, where they extend fibers to the globus pallidus, survive, and persist (*Id.*). Applicants also found that the adult R6-2 HD mouse, a well-established and broadly accepted mouse model of Huntington's Disease, similarly retains a population of dividing subependymal progenitor cells in the striatal wall, and that these cells respond to BDNF overexpression in the HD mouse just as they do in the normal rat, by generating neurons that depart the subependyma, and enter the striatum to integrate as medium

spiny striopallidal neurons (*Id.*). Applicants then found that when the enabling neurogenic effects of BDNF are supplemented by a concurrent suppression of gliogenesis, in the present case using noggin, an antagonist of the pro-gliogenic bone morphogenetic proteins, the number of new neurons added to the treated subject's neostriatum is significantly and substantially increased (*Id.*). This increase proved sufficient to improve both the motor performance and survival of AdBDNF/AdNoggin-co-treated R6-2 mice, relative to their untreated R6-2 controls (*Id.*). Applicants believe that these findings offer great promise for using neuronal induction from endogenous progenitor cells as a feasible and effective therapeutic strategy in Huntington's Disease, a disease that is otherwise presently untreatable and both inevitably and rapidly fatal (*Id.*).

For all of these reasons, it is submitted that the rejection under 35 U.S.C. § 112 (1st para.) for lack of enablement should be withdrawn.

The rejection of claims 1-5, 7, 13-17, and 19 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,071,889 to Weiss, et. al., ("Weiss") is respectfully traversed.

Weiss teaches a method of inducing proliferation of a multipotent neural stem cell by administering various growth factors as proteins *per se* or as nucleic acids encoding such proteins. Although Weiss lists BDNF amongst numerous other growth factors as being suitable for carrying out the subject procedure, there is no evidence of what growth factors might specifically be competent to cause directly infected subependymal cells to migrate out into the striatum, and hence to differentiate into neuronal cells, no establishment of an appropriate means of delivery, no assessment of whether neurons or glia might be generated through this approach, no indication of what neuronal phenotypes might be induced, no specific evidence that medium spiny neurons of the caudate and putamen might be so induced, no indication of whether newly induced neurons might extend fibers to efferent targets, no indication that any such neurons so induced and integrated might assume functional competence, no assessment of what growth factors or combinations thereof might be sufficient to achieve therapeutic endpoints, and no assessment or prediction of what appropriate disease targets for such strategies might be. Overall, Weiss fails to posit, specify or prove how growth factor addition to the adult brain might cause the specific addition of medium spiny pallidal projection neurons to the adult caudate nucleus and putamen.

Since Weiss does not provide an enabling disclosure of the present invention nor teach the features being claimed, it is not anticipatory. Therefore, the rejection of claims 1-5, 7, 13-17, and 19 under 35 U.S.C. § 102 based on Weiss should be withdrawn.

The rejection of claims 1-4, 7, 13-16, and 19 under 35 U.S.C. §102(a) as anticipated by Benraiss, et. al., "*In Vivo* Transduction of the Adult Rat Ventricular Zone with An Adenoviral BDNF Vector Increases Neuronal Production and Recruitment to the Olfactory Bulb", Soc. Neurosci. 25: 413.3 (1999) ("Benraiss"), as evidenced by Weiss, is respectfully traversed.

Benraiss only teaches addition of neurons to the olfactory bulb. In the outstanding office action, the PTO asserts that these features are inherently taught by Benraiss as evidenced by Weiss. However, as demonstrated *supra*, the above-identified features are not taught by Weiss.

Furthermore, Benraiss is not prior art. As demonstrated in ¶¶ 3-6 of the accompanying Fourth Declaration of Steven A. Goldman, M.D., Ph.D. Under 37 C.F.R. § 1.132, the co-authors of Benraiss besides Steven A. Goldman and Abdellatif Benraiss are not inventors of the claimed invention. Therefore, Benraiss is not prior art under 35 U.S.C. § 102(a) and the rejection based on Benraiss must be withdrawn.

The rejection of claim 1, 6, 13, and 18 under 35 U.S.C. § 103 for obviousness over Weiss in view of U.S. Patent No. 5,965,440 to Reeves is respectfully traversed. Reeves is cited as teaching an inducible promoter. However, Reeves does not overcome the above-noted deficiencies of Weiss. Accordingly, the rejection based on the combination of Weiss and Reeves should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 2, 2004

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